II. REMARKS

Formal Matters

Claims 34-38 and 40-114are pending after entry of the amendments set forth herein.

Claims 34-38 and 40-86 were examined and were rejected.

Claims 34 and 47 are amended. The amendments to the claims were made solely in the interest of expediting prosecution, and are not to be construed as acquiescence to any objection or rejection of any claim. Support for the amendments to claims 34 and 47 is found in the claims as originally filed, and throughout the specification, in particular at the following locations: page 13, lines 10-11; page 22, lines 14-16; page 23, lines 3-5; and Example 2, page 52, line 22 to page 53, line 11. Accordingly, no new matter is added by these amendments.

Claims 87-114 are added. Support for new claims 87-114 is found in the claims as originally filed, and throughout the specification, including the following exemplary locations: claims 87, 88, 101, and 102: page 13, lines 2-5; page 21, lines 13-16; Example 11, page 66, line 22 to page 67, line 10; and Figure 8; claims 89 and 103: page 21, lines 13-16; claims 90 and 104: page 54, lines 23-24; claims 91 and 105: page 55, lines 20-21; claims 92 and 106: page 13, line 11; claims 93 and 107: page 8, lines 15-19; claims 94, 96, 108, and 109: page 13, lines 7-8, and page 54, Table 1; claims 95 and 110: page 13, lines 5-7; and claims 96-100, and 110-114: page 15, lines 1-10. Accordingly, no new matter is added by these new claims.

Applicants respectfully request reconsideration of the application in view of the remarks made herein.

Rejection under 35 U.S.C.§112, first paragraph

Claims 34, 36, 37, 43-47, 49, 50, and 54-58 were rejected under 35 U.S.C.§112, first paragraph, as allegedly failing to comply with the written description requirement.

The Office Action stated that the claims are directed to a genus of DNA molecules encoding any hyaluronidase polypeptide from plasma. The Office Action stated that the specification teaches only a partial structure of a single representative species of a plasma hyaluronidase polypeptide; and that the specification fails to describe any other representative species by any identifying characteristics or properties other than the functionality of hyaluronidase polypeptide. Applicants respectfully traverse the rejection.

The Office Action stated that the specification teaches only a partial structure of a single representative species of a plasma hyaluronidase polypeptide. However, as the Office Action acknowledged, the specification teaches two plasma hyaluronidase amino acid sequences: SEQ ID NOs:1 and 3.

The Office Action stated that the claims encompass not only the two plasma hyaluronidases described in the specification, but also any enzyme with or without hyaluronidase activity from any source. However, the claims recite that the plasma hyaluronidase polypeptide is "enzymatically active." As such, the claim language excludes plasma hyaluronidase polypeptides that are not enzymatically active.

The Office Action stated that the claimed hpHases encompass hpHAse with substitutions, deletions, and additions, as defined in the specification; and that this definition renders the claims beyond the scope of what has been described, since hyaluronidases other than plasma hyaluronidases that exhibit hyaluronidase activity are also encompassed by this definition. However, the instant specification provides ample description of human plasma hyaluronidase (hpHAse) polypeptides; and describes a number of identifying features of the enzyme. Specification, page 13, line 2 to page 14, line 4. The specification states that the term hpHAse encompasses polypeptides having amino acid sequences that are modified relative to a naturally-occurring amino acid sequence of hpHase due to amino acid substitution, deletion, and/or addition. Specification, page 13, line 25 to page 14, line 1. Furthermore, as noted above, the specification provides **two** amino acid sequences of hpHAse polypeptides. Specification, page 13, lines 15-25; page 33, lines 9-11; page 33, lines 23-29; and SEQ ID NOs:1 and 3.

Applicants submit that, given 1) the disclosure of two hpHAse polypeptide amino acid sequences; 2) the high skill level of those in the art with respect to identifying variants of polypeptides; and 3) the disclosure in the specification of several identifying features of hpHAse polypeptides, those skilled in the art would reasonably conclude that the Applicants had possession of the claimed invention.

Nevertheless, and solely in the interest of expediting prosecution, claims 34 and 47 are amended to recite that the hpHAse polypeptide partitions into a non-ionic detergent-rich phase at a temperature above about 25°C.

Conclusion as to the rejection under 35 U.S.C.§112, first paragraph

Applicants submit that the rejection of claims 34, 36, 37, 43-47, 49, 50, and 54-58 under 35 U.S.C. §112, first paragraph, has been adequately addressed in view of the remarks set forth above. The Examiner is thus respectfully requested to withdraw the rejection.

Rejection under 35 U.S.C.§102(b)

Claims 34-38 and 40-58 were rejected under 35 U.S.C.§102(b) as allegedly anticipated by Affify et al. ((1993) *Arch. Biochem. Biophys.* 305:434-441; "Afify").

The Office Action stated that Afify discloses the purification of a hyaluronidase from fresh human serum to apparent homogeneity. The Office Action stated that Afify's enzyme is active and purified to apparent homogeneity. Applicants respectfully traverse the rejection.

Purification of hpHAse

The instant invention relates to highly purified hpHAse. The hpHAse is purified to a degree not previously disclosed. The material discussed in Afify is a crude preparation, and as such contains plasma protein contaminants. Indeed, Afify indicates that the hpHAse composition discussed therein exhibited a specific activity of only 53.3 units per mg protein. Afify, page 438, Table 1. Afify does not disclose a composition comprising a hpHAse that is purified to a degree disclosed in the instant application, where the hpHAse is substantially pure. Accordingly, Afify cannot anticipate the instant invention as claimed.

Furthermore, as discussed in the accompanying Declaration of Robert Stern, provide herewith as Exhibit 1, human serum hyaluronidase was not purified to apparent homogeneity, as asserted by Afify; instead, human serum hyaluronidase represented less than 1% of the total protein in the preparation identified by Afify as purified human serum hyaluronidase. This is because human plasma hyaluronidase is present in human serum at concentrations that are too low to give rise to the amount of serum hyaluronidase asserted by Afify from only 1.2 ml serum. Indeed, the protein that is shown in Figure 3B of Afify, and identified in the legend of Figure 3B as "purified human serum hyaluronidase, proved upon amino acid sequence of the N-terminus of protein extracted from the band to be human serum albumin. That the protein preparation asserted by Afify to be purified human serum

hyaluronidase consisted primarily of human serum albumin is not surprising, in view of the abundance of albumin in human serum.

Specific activity

The Office Action stated that claims 40, 42, 52, and 53 are rejected, because the units used to define specific activity of the hyaluronidase in Afify differs from the units used to define specific activity in the instant application; and that Applicants have not provided a Declaration regarding the relationship between the units.

As discussed in the accompanying Declaration of Robert Stern, Afify used a different method to determine enzyme activity from the method described in the instant application. Afify used a method referred to in the Declaration as the "Stern and Stern" method, while the method used in the instant application is referred to as the "Frost and Stern" method. As explained in the Declaration of Robert Stern, there are approximately 6 (Stern and Stern) Units for every (Frost and Stern) Unit. However, conversion is not required to evaluate the purity of the preparations described by Afify and those described in the instant application. As discussed above, and in the Declaration of Robert Stern, human serum hyaluronidase was not purified to apparent homogeneity, as asserted by Afify; instead, human serum hyaluronidase represented less than 1% of the total protein in the preparation identified by Afify as purified human serum hyaluronidase. Accordingly, Afify cannot anticipate claims 34-38 and 40-58.

Conclusion as to the rejection under 35 U.S.C.§102(b)

In view of the facts presented above, Afify does not disclose or suggest a composition comprising substantially pure, enzymatically active hpHAse, as claimed. Accordingly, Afify cannot anticipate claims 34-38 and 40-58.

Applicants submit that the rejection of claims 34-38 and 40-58 under 35 U.S.C. §102(b) has been adequately addressed in view of the remarks set forth above. The Examiner is thus respectfully requested to withdraw the rejection.

Rejection under 35 U.S.C.§103(a)

Claims 59-86 were rejected under 35 U.S.C.§103(a) as allegedly unpatentable over Baumgartner et al. ((1988) *Reg. Cancer Treat.* 1:55-58; "Baumgartner") in view of Afify.

The Office Action stated that Baumgartner teaches the use of a hyaluronidase composition in a Phase I trial in chemoresistant loco-regional malignant disease. The Office Action stated that one of

ordinary skill in the art would be motivated to use the purified hyaluronidase of Afify for the treatment of malignant disease such s the disease disclosed by Baumgartner. The Office Action concluded that it would have been obvious to prepare a composition of the protein of Afify together with a pharmaceutical carrier. Applicants respectfully traverse the rejection.

Baumgartner discusses use of **bull testis hyaluronidase**, not human plasma hyaluronidase. Bull testis hyaluronidase and human plasma hyaluronidase have different molecular, immunologic and biochemical properties. Baumgartner states that the bull testis hyaluronidase used was highly purified. Baumgartner, page 55, column 2, second paragraph under "Materials and Methods." There is no mention in Baumgartner of human plasma hyaluronidase, much less a pharmaceutical formulation comprising human plasma hyaluronidase. There is no motivation in Baumgartner to prepare a formulation comprising substantially pure human plasma hyaluronidase and a pharmaceutically acceptable carrier.

Afify does not cure the deficiency of Baumgartner. As discussed above, Afify does not disclose a composition comprising substantially pure, enzymatically active hpHAse. Accordingly, Baumgartner, alone or in combination with Afify, cannot render claims 59-86 obvious.

Applicants submit that the rejection of claims 59-86 under 35 U.S.C. §103(a) has been adequately addressed in view of the remarks set forth above. The Examiner is thus respectfully requested to withdraw the rejection.

III. CONCLUSION

Applicants submit that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number UCSF-088 CON2.

Respectfully submitted,
BOZICEVIC, FIELD & FRANCIS LLP

Date: Nov. 17, 2005

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